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Survival of Non-Hodgkin Lymphoma Patients with and without HIV-Infection in the Era of Combined Antiretroviral Therapy

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Abstract

Objective—To investigate the survival outcomes for non-Hodgkin lymphoma (NHL) in HIV-infected vs. -uninfected patients from the same integrated health care system, and to identify prognostic factors for HIV-related NHL in the era of combined antiretroviral therapy (cART).

Design—Cohort study.

Methods—Incident NHL diagnosed between 1996–2005 were identified from members of Kaiser Permanente (KP) California Health Plans. Two-year all-cause and lymphoma-specific mortality by HIV status were examined using multivariable Poisson regression. Among HIV-infected patients, prognostic factors of demographics, lymphoma- and HIV-related characteristics for the same outcomes were also examined.

Results—A total of 259 HIV-infected and 8,230 HIV-uninfected incident NHL cases were evaluated. Fifty-nine percent of HIV-infected patients died within 2 years after NHL diagnosis, compared to 30% of HIV-uninfected patients. HIV status was independently associated with a doubling of 2-year all-cause mortality (Relative Risk=2.0, 95% Confidence Interval=1.7–2.3). This elevated mortality risk for HIV-infected patients was similar for all race groups, lymphoma stages and histologic subtypes. HIV-infected patients with CD4 cell count <200/mm³ and/or prior AIDS-defining illness were also at increased risk for lymphoma-specific mortality compared to HIV-uninfected patients. Among HIV-infected NHL cases, significant prognostic factors for overall mortality included prior AIDS-defining illness and Burkitt's subtype.

Conclusions—HIV-infected patients with NHL in the cART era continue to endure substantially higher mortality compared with HIV-uninfected patients with NHL. Better management and therapeutic approaches to extend survival time for HIV-related NHL are needed.

Keywords

HIV infection; non-Hodgkin lymphoma; prognostic factors; antiretroviral therapy; mortality

INTRODUCTION

HIV-infected persons continue to endure a significantly elevated risk for developing non-Hodgkin lymphoma (NHL) compared to the general population in the era of combined

antiretroviral therapy (cART) [1,2]. However, substantial improvements in survival of HIV-related NHL have been reported [3,4]. While several clinical studies suggested comparable survival of patients with HIV-related NHL treated with cART and chemotherapy to that of high grade NHL in HIV-uninfected individuals [3,5–7], these studies often included highly selected patient populations from clinical trials or tertiary clinical centers, which may have limited generalizability. Furthermore, differential access to healthcare by HIV infection status may also introduce confounding. To address these limitations, we sought to determine the association between HIV infection status and mortality outcome after NHL diagnosis in the cART era in an insured, population-based setting of Kaiser Permanente (KP) California, an integrated health care organization. Prognostic factors in HIV-related NHL were also examined.

METHODS

Study Population

KP is the largest managed care organization in California, serving over 6 million ethnically and socioeconomically diverse members. Incident cases of NHLs diagnosed between 1996 and 2005 were identified from KP's SEER (Surveillance, Epidemiology and End Result)-affiliated cancer registries using SEER recodes 33040, 33041, 33042. The histologic subtypes of NHL were identified using ICD-O-3 histology codes 9678–9680 and 9684 for diffuse large B-cell lymphoma (DLBCL), codes 9687 and 9826 for Burkitt's lymphoma, and codes 9690, 9691, 9695 and 9698 for follicular lymphoma. Central nervous system (CNS) involvement was identified using ICD-O-3 site code C70.x, C71.x, C72.x. The cancer registries also provided date of diagnosis, race/ethnicity, stage, and initial course of therapy (e.g., chemotherapy).

HIV-infection status for incident NHL cases was ascertained via record linkage with the KP HIV registries using the patient's unique medical record number. The sensitivity and specificity of the KP HIV registry are estimated to be $\geq 95\%$ and $\geq 99\%$, respectively. Patients included in the HIV registries were initially screened using electronic databases, followed by chart review and/or confirmation with clinical staff at the corresponding medical centers. This study was approved by the KP California Institutional Review Boards.

Outcome Assessment

The primary and secondary endpoint of interest was two-year all-cause mortality and two-year lymphoma-specific mortality after NHL diagnosis, respectively. Causes and dates of death were ascertained from KP hospital death and membership files, California State death certificates, and Social Security administration death files. Lymphoma-specific deaths were identified from California State death certificates using ICD-9 (200, 201, 202; for deaths prior to 1999) and ICD-10 codes (C82, C83, C84, C85, C88, C91, C96, and in addition, B21.1, B21.2, C82, C83, C85 for HIV-infected subjects; for deaths in 1999 and forward). Fourteen deaths (3 HIV-infected, 11 HIV-uninfected) were excluded from the secondary analysis of lymphoma-specific mortality due to missing information on cause of death.

Measurements of Other Covariates

Data for several additional covariates of interest were collected from KP's electronic medical databases. Charlson's comorbidity index [8] was calculated using inpatient diagnosis codes and modified to exclude the diagnosis of AIDS. HIV-specific characteristics examined included HIV transmission risk group and prior AIDS-defining illness (both ascertained from the HIV registry), prior cART use (defined by DHHS published guidelines [9] and captured by KP pharmacy databases), CD4 cell count and HIV RNA level (obtained

from KP laboratory databases). All characteristics were measured at the time of NHL diagnosis.

Statistical Analysis

Distributions of demographics, lymphoma-related and HIV-related characteristics and their univariate associations with mortality outcomes were calculated by HIV-infection status. To study the association between HIV infection status and mortality outcomes, multivariable Poisson regression with robust error variance was used to directly estimate the relative risk (RR) [10]. Factors associated with HIV infection status and two-year mortality in the univariate analyses with p -value <0.10 were included in the multivariable analyses (these included year of diagnosis, age, gender, race/ethnicity, Charlson's index, stage, NHL histology subtype, and CNS involvement). The impact of adjusting for initial treatment of chemotherapy was also considered in a separate model. Stratified analyses were then performed for: (1) white and non-white race; (2) lymphoma stages I/II and stages III/IV; and (3) DLBCL, Burkitt's lymphoma, and other NHL histologic subtypes. HIV-infected patients were also stratified by CD4 cell count ($<200/\text{mm}^3$ and $\geq 200/\text{mm}^3$) at NHL diagnosis and whether NHL was the initial AIDS-defining illness (i.e. no prior AIDS-defining illness) and compared mortality to HIV-uninfected patients.

Among HIV-infected NHL patients, the prognostic value of year of diagnosis, age, gender, race/ethnicity, Charlson's index, stage, NHL histology subtype, CNS involvement, CD4 cell count, HIV RNA level, prior AIDS-defining illness and duration of cART use was evaluated using multivariable Poisson models with robust error variance. Calendar period was included to assess the survival trend of HIV-infected NHL patients. All analyses were conducted using SAS statistical software version 9.1.3 (Statistical Analyses System Inc, Cary, NC, USA).

RESULTS

A total of 259 HIV-infected and 8,230 HIV-uninfected incident NHL cases were identified between 1996 and 2005. Characteristics of the NHL cases differed by HIV-infection status, e.g., HIV-infected NHL cases were more likely to be diagnosed at a younger age and were of black or Hispanic race/ethnicity (Table 1). Fifty-one percent of the HIV-infected patients were diagnosed with a CD4 cell count $<200/\text{mm}^3$; 52% had a prior AIDS-defining illness, and 58% had been previously treated with cART (Table 1).

HIV-infection status and 2-year mortality

Among HIV-infected patients, 59% died within two years after NHL diagnosis, compared to 30% of HIV-uninfected patients (Table 2, top). Of deaths among HIV-infected patients, 58% were lymphoma-related, compared to 76% of deaths in HIV-uninfected patients (Table 2). In the multivariable analyses, HIV-infection status was associated with a doubled 2-year all-cause mortality risk ($\text{RR}=2.0$, 95% confidence interval: 1.7–2.3, $p<0.001$, Table 2). Further adjusting for the initial treatment of chemotherapy after NHL diagnosis did not materially affect the results [$\text{RR HIV+}=1.6$ (1.4, 1.8)]. When HIV-infected patients were further categorized by their CD4 cell count levels and prior clinical AIDS status, elevated all-cause mortality risk compared with HIV-uninfected cases was observed among all subgroups examined (Table 2). In the stratified analyses, the elevated mortality risk for HIV-infected patients was consistently observed across race groups, NHL stages and histologic subtypes (Table 2).

HIV-infected patients were also at increased risk for 2-year lymphoma-specific mortality ($\text{RR}=1.4$ (1.1–1.7), $p=0.001$, Table 2). The risk for lymphoma-specific mortality was

particularly high for those with CD4 cell count $<200/\text{mm}^3$ and/or prior AIDS-defining illness. On the other hand, those who had CD4 cell count $\geq 200/\text{mm}^3$ and no prior AIDS-defining illness appeared to have comparable lymphoma-specific mortality with that of HIV-uninfected patients (RR=1.1 (0.7–1.9), $p=0.66$).

Prognostic factors for mortality in HIV-related NHL

Among HIV-infected cases, Burkitt's lymphoma [RR=1.3 (1.0–1.7)] and prior AIDS-defining illness [RR=1.4 (1.1–1.9)] were significantly associated with an increased all-cause mortality. In addition, non-white race [RR=1.2 (1.0–1.5)], low CD4 cell count ($<200/\text{mm}^3$) at NHL diagnosis [RR=1.2 (1.0–1.6)] and other non-DLBCL histologic subtype [RR=1.2 (1.0–1.6)] also appeared to be associated with elevated all-cause mortality ($p<0.10$). We observed no calendar era changes in overall mortality for these cases. For lymphoma-specific mortality, none of the factors examined were statistically significant prognostic factors, although some demonstrated similar magnitude of RR as in the analysis for all-cause mortality (data not shown).

DISCUSSION

Our study, spanning a 10-year period since 1996, represents one of the largest to include HIV-infected and HIV-uninfected NHL cases identified from the same health system. We observed a 2-year mortality of 60% for HIV-infected NHL patients, a rate that is comparable to those seen in other observational studies (55%–78%) in the cART era [11–14]. We found that overall, HIV-infected NHL patients continued to have a significantly elevated all-cause and lymphoma-specific mortality compared with NHL patients in the general population. However, HIV-infected patients with better controlled HIV disease, i.e., those whose NHL was the first AIDS-defining illness and was developed with a CD4 cell count level of $200/\text{mm}^3$ or greater did not have an increased risk for lymphoma-specific mortality compared to HIV-uninfected patients. This finding supports aggressive HIV disease management strategy for patients infected with HIV and potentially earlier start of cART [15,16].

A previous study found similar survival for HIV-infected and HIV-uninfected NHL patients when response to chemotherapy was adjusted [17]. The authors concluded that the lower complete remission rate achieved by the HIV-infected patients was the cause for the inferior survival for HIV-infected patients. It is possible that the low CD4 cell counts, which can be seen with advanced HIV disease, may be a predictor for undesirable treatment response or toxicity. However, studies evaluating the relationship of CD4 cell count and lymphoma treatment response were mixed [18,19] [6,20]. Future studies should further investigate the effect of HIV disease management on NHL treatment experience.

We found that non-DLBCL lymphoma histologic subtype, prior AIDS-defining illness, non-white race and CD4 cell count $<200/\text{mm}^3$ were prognostic factors for all-cause mortality in HIV-infected patients. The prognostic role of lymphoma characteristics in HIV-infected NHL has been consistently reported in the cART era [18,21–23]. However, contrary to the literature, more advanced stage disease was not a predictor for all-cause mortality among HIV-infected patients. The prognostic role of HIV disease factors (such as CD4 cell count, HIV RNA level, and cART use) in NHL has been less clear [18]. Several population-based studies of HIV-related NHL, including the present one, reported low CD4 cell count and prior AIDS-defining illness to be important prognostic factors in the cART era [11,13,23]. On the other hand, use of cART prior to NHL diagnosis was not predictive of overall survival in this study as well as others [12–14,24].

There are several potential limitations in our study that should be considered when interpreting our results. Due to the observational study design, we did not have information

on CD4 cell counts or HIV RNA levels at NHL diagnosis for many HIV-infected cases (Table 1), which could potentially have resulted in bias if survival was different for cases with and without such measurements. Another potential limitation came from the use of death certificate to determine lymphoma-specific death. As it was possible that some of the NHL-related deaths were vaguely coded with an underlying cause of HIV/AIDS, results for lymphoma-specific mortality should be interpreted with caution. Finally, generalizability of our results to persons without health insurance may be limited, or to other healthcare systems that do not have an integrated healthcare model.

In conclusion, our study showed a poor overall survival, approaching only 40% for HIV-infected patients after NHL diagnosis in the cART era, with no clear improvement over the 10-year study period. However, HIV-infected patients with higher CD4 cell counts and no prior AIDS-defining illness had a similar risk for lymphoma-specific death compared to NHL in the general population. These results emphasize the importance in preserving the immune function during the course of HIV disease management, and further evaluating optimal treatment options for HIV-infected NHL patients with severely suppressed immunity, which account for 50% of the HIV-related NHL in the cART era.

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Chao C led the study design, data analysis and manuscript writing. Xu L performed the statistical analysis. Leyden W and Tang B performed data collection. Abrams D, Horberg M, Towner W, and Klein D provided clinical inputs and critical revision of the manuscript. Silverberg M conceptualized the study and critically revised the manuscript. All authors contributed to the writing of the manuscript.

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Table 1

Distribution of NHL case characteristics by HIV status

	HIV-infected NHL (N=259)	HIV-uninfected NHL (N=8230)	p value
	Number (%)		
Year of diagnosis			
1996–1999	76 (29.3%)	1804 (21.9%)	
2000–2002	102 (39.4%)	3087 (37.5%)	<0.01
2003–2005	81 (31.3%)	3339 (40.6%)	
Age at diagnosis (years)			
<40	67 (25.9%)	565 (6.9%)	
40–59	167 (64.5%)	2331 (28.3%)	<0.01
≥60	25 (9.7%)	5334 (64.8%)	
Gender, Male	248 (95.8%)	4383 (53.3%)	<0.01
Race/Ethnicity			
White	145 (56.0%)	5902 (71.7%)	
Black	33 (12.7%)	530 (6.4%)	<0.01
Asian	9 (3.5%)	717 (8.7%)	
Hispanic	72 (27.8%)	1041 (12.7%)	
Charlson's index excluding AIDS			
0	173 (66.8%)	6396 (77.7%)	
1–4	82 (31.7%)	1638 (11.9%)	<0.01
5+	4 (1.5%)	196 (2.4%)	
Stage at diagnosis			
I	56 (21.6%)	2418 (29.4%)	
II	45 (17.4%)	1303 (15.8%)	0.05
III–IV	134 (51.7%)	3741 (45.5%)	
NHL Subtype			
Diffuse large B-cell	161 (62.2%)	3121 (37.9%)	
Burkitt's	43 (16.6%)	127 (1.5%)	<0.01
Follicular	1 (0.4%)	1577 (19.2%)	
Others [‡]	54 (20.9%)	3405 (41.4%)	
Central nervous system (CNS) involvement	17 (6.6%)	183 (2.2%)	<0.01
Chemotherapy in first 6 months	176 (67.95%)	4840 (58.81%)	<0.01
HIV transmission risk group			
Men who have sex with men	137 (52.9%)	-	
Intravenous drug user	12 (4.6%)	-	
Heterosexual	32 (12.4%)	-	
Other	4 (1.5%)	-	-
CD4 count at time of NHL diagnosis (cells/mm ³ , mean (sd))	191 (162.4)	-	-
<200/mm ³	133 (51.4%)	-	-
≥200/mm ³ , <500/mm ³	72 (27.8%)	-	-

	HIV-infected NHL (N=259)	HIV-uninfected NHL (N=8230)	p value
≥500/mm ³	10 (3.9%)	-	-
Unknown	44 (17.0%)	-	-
HIV RNA level at time of NHL diagnosis (copies/ml, mean (sd))	85805.3 (137695.7)	-	-
<500 copies/ml	33 (12.7%)	-	-
≥500 copies/ml	157 (60.6%)	-	-
Unknown	69 (26.6%)	-	-
Prior AIDS-defining illness	134 (51.7%)	-	-
Prior cART	150 (57.9%)	-	-
Duration of cART treatment among those who were previously on cART (year, mean (sd))	3.2 (2.6)	-	-

Percentage may not add up to 100% due to missing value.

[†] Others include T-cell lymphoma, lymphoma of precursor cell of T-cell, B-cell or unknown origin, chronic lymphocytic leukemia, mantle cell lymphoma, splenic marginal zone lymphoma extranodal, lymphoplasmacytic lymphoma, composite NHL and Hodgkin's lymphoma, and histologic type not specified (NOS).

Table 2

Two-year mortality and relative risk (RR) of HIV-infection status in overall and stratified multivariable analyses

	All-cause mortality	Lymphoma-specific mortality		
	Number of death (%)			
HIV-uninfected	2431 (29.5%)	1844 (22.4%)		
HIV-infected	153 (59.1%)	87 [†] (34.0%)		
HIV+ subgroups vs. HIV−				
	RR (95% CI)	p-value	RR (95% CI)	p-value
HIV-uninfected	Ref		Ref	
HIV-infected	2.0 (1.7–2.3)	<0.001	1.4 (1.1–1.7)	0.001
By HIV-infection subgroups				
HIV-uninfected	Ref		Ref	
HIV-infected				
CD4<200/mm ³ , no prior AIDS-defining illness	2.0 (1.6–2.6)	<0.001	1.6 (1.1–2.2)	0.01
CD4≥200/mm ³ , no prior AIDS-defining illness	1.6 (1.1–2.3)	0.01	1.1 (0.7–1.9)	0.66
CD4<200/mm ³ , prior AIDS-defining illness	2.4 (2.0–2.9)	<0.001	1.6 (1.1–2.2)	0.01
CD4≥200/mm ³ , prior AIDS-defining illness	1.8 (1.4–2.4)	<0.001	1.4 (1.0–2.1)	0.09
Stratified analyses				
HIV+ vs. HIV−				
Race				
White	1.9 (1.6–2.3)	<0.001	1.4 (1.1–1.9)	0.01
Non-white	2.0 (1.7–2.4)	<0.001	1.3 (0.9–1.8)	0.16
Stage at diagnosis				
I–II	2.9 (2.3–2.7)	<0.001	2.0 (1.4–2.8)	<0.001
III–IV	1.6 (1.3–1.8)	<0.001	1.2 (0.9–1.5)	0.28
NHL subtype				
Diffuse large B-cell	1.8 (1.5–2.1)	<0.001	1.3 (1.0–1.6)	0.07
Burkitt’s	2.0 (1.3–2.9)	<0.001	1.3 (0.8–2.2)	0.36
Others	2.5 (1.9–3.2)	<0.001	1.9 (1.3–1.9)	0.002

Models adjusted for year of diagnosis (1996–1999, 2000–2002, 2003–2005), age (<40, 40–59, ≥60 years), gender, race/ethnicity (white, black, Asian, Hispanic, other/unknown), modified Charlson's index excluding AIDS (0, 1–4, ≥5), stage of NHL (I–II, III, unknown), CNS involvement, NHL histologic subtype (diffuse large B-cell, Burkitt's, follicular, others). For the stratified analyses, the stratification factor was not included in the model.

[†] Other causes of death for HIV-infected patients included HIV/AIDS-related events (n=58), myocardial infarction (n=2), respiratory distress syndrome (n=1), myeloid leukemia (n=1), injury (n=1) and unknown (n=3).